DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
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CBER – 06–003

DEC 15 2005

Warning Letter

Nkossi C. Dambita, M.D., Chair
Institutional Review Board
Baltimore City Health Department
210 Guilford Avenue
Baltimore, Maryland 21202

Dear Dr. Dambita:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from August 22 through 29, 2005. FDA investigator Stephanie Shapley conducted an inspection of the Baltimore City Health Department (BCHD) Institutional Review Board (IRB) to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies using investigational products and for the protection of human subjects. At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you.

We have determined that the IRB significantly violated regulations governing the operation and responsibilities of IRBs as published under 21 CFR 50 and 56 (available at http://www.access.gpo.gov/nara/cft/index.html). The applicable provisions of the CFR are cited for each violation.

1. **The IRB failed to follow its written procedures for conducting the review of research, including periodic review. [21 CFR § 56.108(a)].**

   The IRB failed to recognize that applications submitted as "annual renewals" and "amendments" under study [redacted] by the [redacted] laboratory actually represented new studies that required full review. In allowing the [redacted] to submit those new studies as "annual renewals" and "amendments," the IRB failed to follow its policies and procedures entitled "New Study Application Review Procedure." Those policies required the IRB to assign a new tracking number to [redacted] proposed new studies, and required full committee review. However, the IRB did not notice that the studies represented

different studies using different investigational devices and sponsors. As a result, the IRB approved those studies incorrectly as continuations of a previously approved study under the same tracking number. Consequently, studies were conducted at your institution without proper review and approval.

The [redacted] laboratory submitted the new study entitled [redacted] on 11/15/00. The IRB assigned the study tracking number of [redacted] and approved the study on 2/05/01.

Under the same tracking number, the clinical investigator later submitted an "amendment" to [redacted] that was, in fact, a new protocol entitled [redacted]. The IRB approved this "amendment" request via expedited review process on 3/11/02 without realizing that it was a new protocol that should have been assigned a new tracking number.

On two more occasions, the laboratory submitted two more new studies as "annual renewal applications" for study [redacted]. The IRB file for [redacted] contains the study entitled [redacted] as well as the signed agreement between the clinical investigator and the different sponsor, which was submitted on 2/27/03. On 1/22/04 the investigator also submitted an "annual renewal application" with the study entitled [redacted] from a different sponsor. The IRB records show that these protocols were approved as "renewals" of [redacted] on 3/21/03 and 2/27/04. The IRB also approved the two different consent forms naming these two separate sponsors.

2. **The IRB failed to conduct continuing review of research at intervals appropriate to the degree of risk. [21 CFR § 56.109(f)].**

There were no records in the IRB's file to show that the IRB conducted continuing review of the following six studies at intervals appropriate to the degree of risk, but not less than once per year. These new studies, which were approved as renewals and amendments incorrectly, should have been reviewed at least annually as required by the regulation.

Study #	Protocol	Approval Date	Sponsor
[redacted]	[redacted]	1/26/01	[redacted]
		3/11/02	
		11/09/01	
		3/21/03 – Only the approved consent form is in file	
		3/24/04 – Only the approved consent form is in file	
		No Record of Approval	

3. The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115].

A. The minutes of the IRB meetings do not document all actions taken by the IRB, and the vote on those actions, including the number of members voting for, against, and abstaining. The minutes from meetings on 3/21/02, 5/9/03, 7/18/03, 10/14/03, and 7/12/04 all failed to show the actions taken and the members voting for, against, and abstaining.

B. Meeting minutes do not always record the basis for requiring changes in or disapproving research, and a summary discussion of controverted issues and their resolution. For example, the meeting minutes for the 07/18/03 meeting showed that eight new proposals, three annual renewals, and two amendments were approved without documenting the discussions and the basis for approval.

C. The IRB failed to maintain records of the current members' earned degrees, representative capacity, indications of experience sufficient to describe each member's chief anticipated contribution to IRB deliberations, and any employment or other relationship between each member and the institution.

D. Four of the ten IRB membership rosters reviewed during the inspection failed to include the date and the year. The roster for 2004 listed the title, but not the name, for one of the alternate members.

E. In an undated letter, [redacted] laboratory requested an IRB approval stamp on a consent form for the study entitled [redacted] under [redacted] and the IRB Chair approved the form on 2/27/04. However, the IRB file contains only the second page of the approved form and there is no record to show that the approved consent form is in compliance with the requirements of 21 CFR 50.25.

4. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB were present. [21 CFR § 56.108(c)].

A. According to the IRB's written procedures, the IRB consists of ten members, and the IRB Chair is not permitted to vote unless there is a tie. The section of IRB's policy entitled IRB Chair's Duties, Authorities, and Responsibilities, under number 23, state that the IRB chair should "Vote on IRB business only in case of a tie vote by the HSRC". The IRB failed to establish a majority of members at four meetings. On 3/21/03 and 5/9/03 there were five members in attendance, not including the IRB Chair. On 1/14/05 and 5/13/05 there were three and four members in attendance, respectively, not including the Chair. During the above days, the IRB voted to approve new studies, annual renewals, and amendments.

B. The IRB allowed non-members to vote on research projects. The individuals listed in the table below voted during IRB meetings even though they were not listed on the IRB's membership roster for the corresponding time.

IRB Meeting Date	Individual(s) not Listed on Roster but Listed as Committee Members Present
1/10/03	[redacted]
3/21/03	
7/18/03	
1/09/04	
9/17/04	
1/14/05	
5/13/05	

We note that there were additional instances in which it appears that nonmembers voted at meetings, but the lack of revision dates on the rosters makes it impossible for the IRB to assure the effective date for the membership

rosters. .

5. **The IRB failed to fulfill the requirements for expedited review. [21 CFR § 56.110(b)].**

The IRB approved the re-opening of study [redacted] by expedited review on 1/24/05. The study involved more than minimal risk, in that it used an invasive procedure, and was therefore not eligible for the expedited review approval process. The study was previously terminated per the request of the investigator on 1/05/05. Furthermore, there is no record to show that the IRB members were advised at the next convened meeting, as required by 21 CFR 56.110 (c), that the study was re-opened under the expedited review procedure.

6. **The IRB failed to require that information given to subjects as part of Informed consent is in accordance with the provisions of 21 CFR 50.25. [21 CFR § 56.109(b)].**

The IRB approved four consent forms that did not note the possibility that FDA may inspect the records. This information should have been included on the informed consent documents entitled [redacted]

As part of your response to this letter, please provide documentation of the dates that the alternate members were trained regarding the IRB's operations and human subject protection before they participated in IRB meetings and voted on proposed research, as required by your policy in the section titled " Membership Training."

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility, as well as that of the institution, and the IRB, to conduct a thorough review of the IRB's functions, and to draft appropriate procedures with sufficient detail and clarity to be in compliance with the regulations.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Also, for any plans of action, please include projected completion dates for each action to be accomplished.

Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include FDA prohibiting the approval by your IRB of new studies that are subject to

Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Solomon Yimam
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Telephone: (301) 827-1948

We request that you send a copy of your response to the FDA office listed below.

Sincerely,

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc:

Dr. Joshua Sharfstein
Commissioner of Health
Baltimore City Health Department
210 Guilford Avenue, 3rd Floor
Baltimore, Maryland 21202

Evelyn Bonnin, District Director
Food and Drug Administration
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Baltimore, MD 21215

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1101 Wootton Parkway, Suite 200
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